

REMARKS/ARGUMENTS

With this amendment, claims 1, 6, and 17-19 are pending. Claims 7-13 are withdrawn. Claims 2-5, 14-16, and 20-25 are cancelled. For convenience, the Examiner's rejections are addressed in the order presented in a November 24, 2004 Office Action.

I. Status of the claims

Claim 1 is amended to recite "production of recombinant human α_1 -antitrypsin polynucleotide using semi-continuous culture of transgenic rice cells comprising a heterologous expression cassette comprising a polynucleotide encoding the human α_1 -antitrypsin polynucleotide operably linked to a RAmy3D promoter". Support for this amendment is found throughout the specification, for example, at original claims 4, 5, 9, and 10. In view of this amendment, claims 6 and 17 are also amended to correct antecedent basis. Claim 1 is also amended to recite the step of "isolating the recombinant expression product from the induction medium, wherein the recombinant expression product is a heterologous protein and the induction medium pH increase correlates with a high level of heterologous protein expression." Support for this amendment is found throughout the specification, for example, at page 16, lines 9-10.

II. Claim objections

Claim 25 is objected to for alleged improper dependence from a withdrawn claim. In order to expedite prosecution, claim 25 is cancelled. In view of this amendment, withdrawal of the objection is respectfully requested.

III. Rejections under 35 U.S.C. §112, first paragraph, enablement

Claims 1, 4-6, and 15-25 are rejected for alleged lack of enablement. In order to expedite prosecution, claim 1 is amended to recite "production of recombinant human α_1 -antitrypsin polynucleotide using semi-continuous culture of transgenic rice cells comprising a heterologous expression cassette comprising a polynucleotide encoding the human α_1 -antitrypsin

polynucleotide operably linked to a RAmy3D promoter". In view of this amendment, withdrawal of the rejection under 35 U.S.C. §112, first paragraph is respectfully requested.

IV. Rejections under 35 U.S.C. §103(a)

Claims 1, 4-6, and 15-25 are rejected as allegedly obvious in view of Terashima *et al.*, Fischer *et al.*, and an alleged admission. To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the claims limitations. MPEP§2143. See also *In re Rouffet*, 47 USPQ2d 1453. The court in *Rouffet* stated that "even when the level of skill in the art is high, the Board must identify specifically the principle, known to one of ordinary skill, that suggests the claimed combination." *Rouffet* at 1459. The court has also stated that actual evidence of a suggestion, or teaching, or motivation to combine is required and the showing of a suggestion, or teaching, or motivation to combine must be "clear and particular." *In re Dembiczak*, 50 USPQ2d 1614, 1617 (1999). The Office Action does not provide a *prima facie* case of obviousness.

The Examiner continues to allege that a descriptive passage in the specification is an admission of knowledge of correlation of pH values with protein production among those of skill. Applicants continue to traverse the Examiner's position and assert again that the inventors were the first to demonstrate that an increase in pH levels after a switch to induction medium coincides with the expression of recombinant protein in the induction medium. Applicants refer again to the paragraph cited by the Examiner at page 5, line 7 and to the preceding paragraph beginning at page 4, line 32. The paragraph beginning at page 4, line 32 explains that, when a heterologous protein is expressed using the claimed methods, the pH of the medium increases as expressed protein levels increase and that the pH increase is a convenient indicator of protein production and time for harvest of the heterologous protein. This was the first public disclosure of the correlation between an increase in pH level and an increase in heterologous protein

production. The paragraph goes on to explain that, in embodiment with a starting culture pH of about 5.0, increased protein expression is associated with pH levels above 5.0, or above 5.5, 6.0, 6.5, 7.0, 7.5, or possibly as high as 8.0 or 8.5. Thus, while the final pH level can vary, if the starting pH is, *e.g.*, 5.0, an increased level could be selected from pH levels above 5.0. This point is made in the sentence cited by the Examiner as an alleged admission: "One of skill in the art will recognize that the pH value for optimal protein production will vary with the culture conditions, the type of cells, and the protein produced." The statement that the pH value for optimal protein production will vary with culture conditions *ect.*, describes the understanding of one of skill after learning of the correlation between pH increase and protein production increase. The paragraph continues to describe other conditions where an increase in pH can vary. After one of skill learned of the correlation between an increase in pH level with an increase in protein production, one of skill would thus understand that the increase would depend on variables including, *e.g.*, the starting pH, and medium components. Figure 3 also supports Applicants' interpretation by demonstrating that there is some variability of starting pH levels after addition of induction medium. Compare, *e.g.*, pH levels at induction 1 with those at inductions 2 and 3. Although some variability was seen in the starting induction pH level, the increase in pH consistently correlated with the increase in protein production. The statement cited by the Examiner cannot be interpreted to mean that there was recognition in the field of the novel observation of correlation between increased pH and increased protein production before the filing of the present application.

Applicants have in previous responses discussed in detail the disclosure of Terashima *et al.*, Fischer *et al.*, neither of which teach or disclose monitoring medium pH to determine an appropriate time for harvest of recombinant protein. The references also fail to provide motivation to one of skill to attempt such monitoring. In fact, Fischer *et al.* fail to teach production of any recombinant protein. The Examiner has not provided any reference to remedy the deficiencies of these references and thus, the requirements of a *prima facie* case of obviousness are not met by the Office Action.

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Examining Group 1638

PATENT

In view of the above amendments and remarks, withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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